

Amend claim 43 as follows:

c4 43. (amended) The composition according to claim 42, wherein said associated non-selenium compound is selected from the group consisting of vitamin E, vitamin C, a glutathione precursor, an iron chelator, a copper chelator, copper and zinc.

REMARKS

This application has been amended in a manner that is believed to place it in condition for allowance at the time of the next Official Action.

In the outstanding Official Action, claim 43 was objected to under 37 CFR 1.75(c) as allegedly being of improper dependent form for failing to further limit the subject matter of a previous claim. This rejection is respectfully traversed.

Claim 43 remains dependent on claim 42 and has been amended to recite a composition. Thus, the objection set forth in the Official Action is believed to be obviated by the present amendment.

Claims 25, 29, 37 and 39-40 were rejected under 35 USC 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This rejection is respectfully traversed.

Claims 25 and 37 were rejected for allegedly being confusing. While Applicants contend that claims 25 and 37 are

definite to one of ordinary skill in the art, in the interest of advancing prosecution, claims 25 and 37 have been cancelled.

Claim 29 was rejected for allegedly being unclear for reciting the phrase "modulate more precisely different compartments of said systemic inflammatory reaction". Claim 29 has been amended so this phrase is no longer recited in the claim. Thus, it is respectfully submitted that claim 29 is definite to one of ordinary skill in the art.

Claim 39 was rejected for containing a misspelling of dose. It is believed to be apparent that claim 39 has been amended to correct this informality.

The outstanding Official Action alleged that claim 40 was indefinite for reciting a first treatment "administered during a time period between a first day to fourth day of treatment". The Official Action questioned how could there be a first or fourth day of treatment. In claim 40, line 3, the term "treatment" is replaced by the term "the method". Thus, the time period that is defined in the body of the claim refers to the starting point of the method as a whole. Thus, it is respectfully submitted that claim 40 is definite to one of ordinary skill in the art.

Thus, in light of the present amendment, it is believed that claims 23-24, 26-36 and 39-43 are definite to one of ordinary skill in the art.

As to the publications cited in the outstanding

Official Acton, Applicants respectfully submit that the physiological situations set forth in those publications have no relationship at all with the acute pathological situation targeted by the claimed method, namely the severe form of Systemic Inflammatory Response Syndrome (SIRS).

As disclosed in page 4, lines 3-6 in the present specification, SIRS consists of an acute inflammatory pathology which has been universally defined. The definition of SIRS was set forth by BONE et al. in 1992 during the ACCP/SCCM Consensus Conference Committee. A copy of the report is enclosed.

As specified by BONE et al (1992), severe SIRS is defined as a systemic inflammatory response to a variety of clinical insults. These responses are also defined by BONE et al. (see page 1646, right column, Table 1).

In fact, in the ACCP/SCCM Consensus Conference, a grading of the severity of sepsis was established. The following gradations were established of sepsis, severe sepsis and septic shock. The claimed method relates to the treatment of severe SIRS, that is to say severe sepsis (including septic shock). Thus, the claimed method is directed to patients suffering from severe SIRS and experiencing severe sepsis or septic shock. The method also corresponds to severe SIRS patients with an inflammatory host response to non infectious aggression.

Notably, the severe form of SIRS may be associated with multiple organ dysfunction syndrome or MODS. The definition of

MODS is provided on page 1648, at the beginning of the right column of BONE et al. MODS consists of a highly serious alteration of the physiological situation of patient organs. MODS corresponds to a high risk of mortality, as shown in figures 3-5 of BONE et al (1992).

The various organ failures associated with severe SIRS may be conventionally assessed through a SOFA score, as set forth in Examples 1 to 3 in the present specification. Also enclosed is an article published in 1996 (Intensive Care Med., volume 22: 707-710) which elaborates on the test allowing for the assessment of the universally recognized SOFA score of a determined patient. As set forth in the article (see page 707, left column), multiple organ failure is a major cause of morbidity and mortality in the critically ill patient.

Thus, the severe SIRS pathological situation which is the target of the claimed method relates to severe acute inflammatory disease states associated with a high risk of mortality for the patient, even if said patient is appropriately and timely treated in a specialized intensive care unit (ICU) of a hospital. In contrast to SIRS, which is treated according to the claimed method, the publications cited by the Official Action all relate to the beneficial effects of selenium for enhancing an immune response against various viruses, namely bovine rhinotracheitis virus (Chemical Abstract 108 : 149 240), birnavirus (Chemical Abstract 127 : 171 274), or respiratory

syncytial virus (Chemical Abstract 129 : 134 509) which do not cause SIRS or MODS as defined above. Thus, they represent infections for which no SOFA score can be assessed.

In the outstanding Official Action, claims 23, 25, 26, 27 and 31 were rejected under 35 U.S.C. 102(b) as allegedly anticipated by or, in the alternative, under 35 U.S.C. 103 (a) as allegedly obvious in view of Chemical Abstract 108:149240. This rejection is respectfully traversed.

Applicants respectfully submit that the publication fails to disclose or suggest the claimed invention. The goal of the academic study disclosed in this document was to show that selenium deficiency affects the primary and the secondary humoral immune response of calves challenged with infectious bovine rhinotracheitis virus (IBRV). First, Applicants note that that the study involves depletion of selenium for a first group of studied calves, whereas the second group of studied calves appear to have been fed a diet containing a normal quantity of selenium.

Applicants believe that this study does not relate to the treatment of a specific pathology with selenium, but rather is directed to showing that a depletion in selenium may depress a normal immune response. In fact, the survival survey of the infected calves is measured 70 days after the first challenge with IBRV, which clearly means that the IBRV infection does not lead to an acute chronic inflammatory state of the calves, and in no case to severe SIRS.

Moreover, it is respectfully submitted that the cited publication fails to disclose each and every recitation of the claimed invention. Regarding the selenium doses supplied to the calves, the publication discloses a selenium dose of 0.2 mg/kg of diet. Thus, Applicants believe that the publication does not disclose or suggest administering a daily dose of selenium uptake of 0.2 mg/kg by weight of the patent. Thus, it is respectfully submitted that the Chemical Abstract 108:149240 fails to disclose or suggest the claimed invention.

Claims 23, 25, 26, 27 and 31 were rejected under 35 U.S.C. 102(b) as allegedly anticipated by or, in the alternative, under 35 U.S.C. 103 (a) as allegedly obvious in view of Chemical Abstract 127: 171274. This rejection is respectfully traversed.

Chemical Abstract 127: 171274 studies the role of a nutritional dose of selenium on the cell-immunity of a chicken experimentally infected with birnavirus causing infectious bursal disease (IBD). Applicants note that a nutritional supply of selenium is given to the chicken 39 days before the infectious challenge with birnavirus. Thus, the experimental infectious model illustrated in Chemical Abstract 127: 171274 is distinct from that of septic shock associated with a rapid mortality due to a systemic inflammation.

Applicants also believe that the cited publication fails to disclose each and every recitation of the claimed invention. Chemical Abstract 127: 171274 states that the treated

chicken received a diet containing 0.086 mg/kg of diet of selenium, further supplemented with 0.3 mg/kg of diet (1) or 0.6 mg/kg of diet (2) of selenium. Applicants submit that the selenium doses of Chemical Abstract 127: 171274 only relate to the selenium ratio as regards to the diet weight and do not relate to the chicken's weight.

Thus, while the publication may disclose that a normal nutritional supply of selenium may enhance or maintain the immune resistance of a chicken to viruses, Chemical Abstract 127: 171274 fails to disclose or suggest the claimed invention.

Claims 23, 24, 25, 26, 28, 30 and 31 were rejected under 35 U.S.C. 102(b) as allegedly anticipated by or, in the alternative, under 35 U.S.C. 103 (a) as allegedly obvious in view of Chemical Abstract 129: 134509. This rejection is respectfully traversed.

Chemical Abstract 129: 134509 is concerned with the role of selenium in enhancing the immune resistance of children to respiratory syncytial virus. However, Applicants note that respiratory syncytial viruses do not cause pneumonia or pneumopathy, but rather bronchiolitis. As disclosed, trial subjects were divided into two groups, respectively (i) one with 37 children in routine treatment, (ii) the other 38 children in routine treatment but with a selenium supplement. It should be underlined that no mortality was observed irrespective of the groups of children included in the study, which clearly

demonstrated that the physiological situation did not involve an acute severe inflammatory disease state, as it is the case for severe SIRS.

Rather, this study shows that children that have received a diet supplemented with selenium develop a higher immune resistance to RSV infection in relation to a control group of children fed a normal diet.

Moreover, it is respectfully submitted that the cited publication fails to disclose each and every recitation of the claimed invention. Chemical Abstract 129: 134509 discloses that the immune resistance of children against respiratory syncytial virus can be enhanced by supplementing the children orally with 1 mg sodium selenite on the second day of hospitalization. 1 mg of sodium selenite ($\text{Na}_2\text{SeO}_3 \cdot 5\text{H}_2\text{O}$) contains 330 ug of atomic selenium.

However, claim 23 relates to a method of treatment of adult patients. In addition, Applicants note that the recommended selenium doses administered to children are far higher than doses recommended for adult subjects. Enclosed is a copy of the Recommended Dietary Allowance (10th edition 1989, pages 217-224) for selenium. As specified in page 220, in the last lines of the first full paragraph, the recommended dietary selenium allowance for adults ranges between 55 µg per day to 70 µg per day. In contrast, the second full paragraph of page 220 specifies that the recommended selenium allowance for infants and children is of 15 µg per day, thus 2.14 µg per kilo for a child under one year

of age and weighting a maximum of 7 kg. Transposed to an adult person weighting 75 kg, the recommended selenium allowance for children would lead to a dose of 165 μg per day for an adult. However, if the specified selenium dose is transposed to an adult person, it would be lower than the claimed selenium dose range.

In light of the above, it respectfully submitted that that Chemical Abstract 129: 134509 fails to anticipate or render obvious the claimed method.

Claims 41-43 were rejected under 35 U.S.C. 102(b) as allegedly anticipated by or, in the alternative, under 35 U.S.C. 103 (a) as allegedly obvious in view of WO 98/33495.

The Official Action contends that WO 98/33495 discloses a pill that contains 6.25 mg selenium aspartate and that, consequently, this pill would provide 2.3 mg selenium/pill (one selenium atom per molecule) or even 3.4 mg selenium/pill (two selenium atoms per molecule). The Official Action further contends that selenium aspartate contains one or two selenium atoms per molecule. However, Applicants note that on the same page of the WO 98/33495 publication, it is specified that the amount of selenium aspartate indicated (6.5 mg selenium aspartate), corresponds to 12.5 μg of selenium. Thus, Applicants submit that there is not a strict stoichiometric relationship between selenium atoms and aspartate within the selenium aspartate compound contained in the pill disclosed in the WO 98/33495 publication. When taking into account that the pill

is designed for the treatment of an adult (80 kg), the selenium dose which would be received by the patient supplied with the disclosed pill would be approximately $0.16 \mu\text{g} / \text{kg}$ ($12.5/80$). A selenium dose far lower than the minimal atomic selenium dose specified by the claimed invention.

In the outstanding Official Action, claims 22-33 and 35-43 were rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over the combined teachings of Zimmermann et al, Borner, et al and Chemical Abstract 129:134509 in view of Medline abstract 89032644 and WO 98/33495. This rejection is respectfully supported.

It is respectfully submitted that the proposed combination of references fails to render obvious the claimed invention. At the time the application was filed, applicants respectfully submit that one of ordinary skill in the art would have been deterred against the therapeutic use of atomic selenium at doses higher than 1 mg. Enclosed are six documents which illustrate the high prejudice that one of ordinary skill in the art would have against the use of selenium at the recited ranges of the present invention.

The article of HAJI-MICHAEL et al. (CRIT.CARE.MED., 1998, Volume 26 (9): 1478) specifies that selenium is toxic at doses higher than $600 \mu\text{g}$ per day (paragraph bridging the second and third column). BERGER (1998, NUTR. CLIN. METABOL., volume 12, (SUPPL. 1) : 1997-209), in page 203 of the article, specifies

that the selenium toxicity appears to locate at about 700 µg / day (see page 203, left column, line 4). The summary of the article of SAKURAI et al. (1975, ENVIRON. PHYSIOL. BIOCHEM., volume 5 : 107-118) discloses that the acceptable maximum selenium daily dose is of 500 µg. LEUNG (1995, CLINICAL BIOCHEMISTRY, volume 28 (6) : 561-566) estimates, in page 564, left column, second paragraph, that selenium daily doses ranging from 100 to 600 µg would be suitable whereas selenium doses higher than 1500 µg / day are considered as toxic. COMBS (The role of selenium in nutrition, 1986, ACAD. PRESS. INC., page 511-512) estimates that the maximal acceptable selenium daily dose is 1000 µg and refers to the selenium doses which are considered as non-toxic doses by the food and nutrition board National Research Council, which is 200 µg / day. KOLLER (1986, CAN. J. VENT. RES., volume 50: 297-306) reminds one that the maximal recommended selenium daily dose for a human is 500 µg (see page 297, middle column, second paragraph) and underlines that, from compilation of available data, the maximum tolerable level for selenium in man could be considered in the range of 1000 to 1500 µg / day.

Consequently, the acknowledged maximal daily dose of selenium in an adult human, at the date the invention was made, should be lower than 700 µg for patients undergoing oxidative stress and lower than 1000 µg for a healthy individual. Higher doses of selenium were, at the time the invention was made,

considered toxic for individuals.

As stated by the Official Action, ZIMMERMAN et al. disclose a daily administration of sodium selenite of 1000 µg which is 456 µg of atomic selenium per day. Thus, the daily selenium dose used by ZIMMERMANN et al. is a conventional selenium dose which conforms with the general widely accepted recommendation of 1997.

BORNER et al. disclose administering pentahydrate sodium selenite at a dose of 200 µg for patients weighing less than 15 kg and 500 µg for patients weighing 15-30 kg and 1000 µg for patients weighing more than 30 kg, the treatment consists of a single administration of the above described pentahydrate sodium selenite.

Thus, Applicants submit that ZIMMERMANN et al. and BORNER et al. fail to provide any additional information as regards to the therapeutic use of selenium that would go beyond the general knowledge of one skilled in the art at the time the application was filed. It is believed that one skilled in the art would lack the motivation and a reasonable expectation of success of obtaining the claimed invention by modifying the teachings of of ZIMMERMANN et al. and BORNER et al.

The claimed invention relates to the use of atomic selenium doses up to 1 mg/kg. Selenium doses up to 80 times higher than those which are universally recommended. Thus, applicants believe that ZIMMERMANN et al. and BORNER would

actually lead one away from the claimed invention.

As noted above, Chemical Abstract 129:134509 relates to the nutritional supply of selenium in young children under one year of age, and who are infected with respiratory syncytial virus. A disease which cannot be compared with SIRS. Notably, it is reminded that the control group of children which are not supplemented with selenium do not appear to undergo any risk of mortality, contrary to SIRS, wherein the mortality rate is about 80% in the case of severe sepsis.

Moreover, the selenium doses administered to the treated children strictly conform to the recommended dietary selenium allowance, as already specified above. Thus, Applicants believe that Chemical Abstract 129:134509 fails to remedy the deficiencies of ZIMMERMANN et al. and BORNER et al.

As to the Medline Abstract: 89032644, the publication relates to the selenium concentration in patients affected with uncomplicated viral or bacterial infections. Again, this document does not relate to acute inflammatory states which may be compared to severe SIRS. According to this document, a difference is observed in the serum selenium concentration between the acute phase of the infection and compared with the recovery period. Although a slight depression in the selenium concentration in the acute stage of the infection is considered as significant by the authors, it should be stressed that this statistically significant difference is very minimal. The acknowledged

variability of serum selenium measured is conventionally of 5 µg/L. Classically, a difference of less than 10 µg/L is generally considered as contained within the normal measure of variability range limits.

In contrast, an acute inflammatory disease states, such as severe SIRS, there is a high depression of the serum selenium concentration which decreases the normal reference value of 0.89 µmol/L to 0.20 µmol/L for the patients affected with a severe sepsis, such as a SIRS. Because the infection concerned does not relate to severe SIRS, nor to any pathological situation comparable to SIRS, it flows that these additional publications cannot overcome the deficiencies of ZIMMERMANN et al., BORNER et al. and CHEMICAL ABSTRACT 129:134509, even when combined together.

As noted above, the WO 98/33495 discloses a pill containing selenium aspartate, wherein the content of atomic selenium is 12.5 µg for each pill, thus a very weak selenium dose. Indeed, the WO 98/33495 publication discloses a far lower selenium dose than the other publications cited by the Official Action. Thus, applicants believe that this document also fails to overcome the deficiencies of the other cited documents.

In view of the present amendment and the foregoing remarks, therefore, it is believed that this application is now in condition for allowance, with the claims as presented. Allowance and passage to issue on that basis are accordingly

FORCEVILLE et al. S.N. 09/763,870

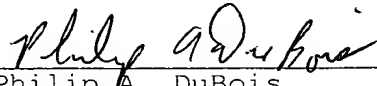
respectfully requested.

Attached hereto is a marked-up version of the changes made to the claims. The attached page is captioned "VERSION WITH MARKINGS TO SHOW CHANGES MADE."

Respectfully submitted,

YOUNG & THOMPSON

By


Philip A. DuBois
Agent for Applicants
Registration No. 50,696
745 South 23rd Street
Arlington, VA 22202
Telephone: 521-2297

January 16, 2003

VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS:

Claim 23 has been amended as follows:

23. (amended) A method for treating [a] an adult patient suffering from severe systemic inflammatory response syndrome [or any state corresponding to a severe acute attack of an inflammatory pathology causing an exacerbation of cytokine secretion], comprising:

administering to said patient an effective amount of a composition comprising at least one molecule containing selenium, wherein said effective amount is a daily dose of a selenium composition containing about 0.025 to 1 mg/kg of atomic selenium.

Claim 29 has been amended as follows:

29. (amended) The method according to claim 23, wherein several molecules containing selenium are used [to modulate more precisely different compartments of said systemic inflammatory reaction].

Claim 39 has been amended as follows:

39. (amended) The method according to claim 35, further comprising administering to said patient an additional treatment of an effective amount of at least one molecule containing selenium, wherein said effective amount is a daily

[does] dose of about 0.025 to 1 mg/kg of atomic selenium is given to said patient.

Claim 40 has been amended as follows:

40. (amended) The method according to claim 35, wherein

said first treatment is administered during a time period between a first day to fourth day of [treatment] the method, and

said subsequent treatment is administered 1 to 20 days after said first treatment.

Claim 43 has been amended as follows:

43. (amended) The [method] composition according to claim 42, wherein said associated non-selenium compound is selected from the group consisting of vitamin E, vitamin C, a glutathione precursor, an iron chelator, a copper chelator, copper and zinc.